

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
30 November 2000 (30.11.2000)

PCT

(10) International Publication Number
WO 00/71116 A1(51) International Patent Classification⁷: A61K 31/40, C07D 207/34

M., Dileep [IN/IN]; Vaishali Apartments, Pocket A-12, 3C, Kalkaji Extension, New Delhi 110 019, Maharashtra (IN).

(21) International Application Number: PCT/IB00/00014

(81) Designated States (national): AE, AL, AM, AT, AU, AZ,

(22) International Filing Date: 6 January 2000 (06.01.2000)

BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,

(25) Filing Language: English

DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

(26) Publication Language: English

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

(30) Priority Data:
775/DEL/99 25 May 1999 (25.05.1999) IN

LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,

(71) Applicant (for all designated States except US): RAN-BAXY LABORATORIES LIMITED [IN/IN]; 19 Nehru Place, New Delhi 110 019, Maharashtra (IN).

RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,

UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,

KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent

(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent

(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,

MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,

GA, GN, GW, ML, MR, NE, SN, TD, TG).

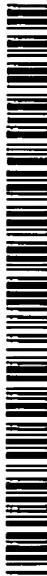
(72) Inventors; and

Published:

(75) Inventors/Applicants (for US only): KUMAR, Yatendra [IN/IN]; U-26/5, DLF Qutab Enclave, Phase - III, Gurgaon 122 001, Haryana (IN). THAPER, Rajesh, Kumar [IN/IN]; B-26, Sunshine Apartments, Block "C", Sushant Lok - I, Gurgaon 122 002, Haryana (IN). KUMAR, S.,

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/71116 A1

(54) Title: PROCESS FOR THE PRODUCTION OF AMORPHOUS ATORVASTATIN CALCIUM

(57) Abstract: A process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises: (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent; (b) adding a non-polar hydrocarbon anti-solvent or adding the dissolved atorvastatin to the non-polar anti-solvent to precipitate out atorvastatin calcium; and (c) removing the solvent by filtration to afford amorphous atorvastatin calcium.

**PROCESS FOR THE PRODUCTION OF
AMORPHOUS ATORVASTATIN CALCIUM**

5

FIELD OF THE INVENTION

The present invention relates to a process for the production of amorphous atorvastatin calcium.

10

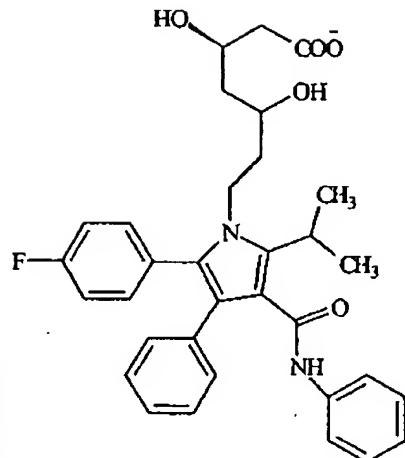
BACKGROUND OF THE INVENTION

Atorvastatin is chemically $[R\text{-(R*},R^*)\text{]-2-(4-fluoro-phenyl)-\beta\text{ dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H pyrrole-1-heptanoic acid.}$ Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. Open dihydroxy carboxylic acid, lactone and various salt forms of atorvastatin have been synthesized.

15

United States Patent 5,273,995, describes that R-form of the ring opened acid form has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. $[R\text{-(R*},R^*)\text{]-2-(4-fluoro-phenyl)-\beta,\ \delta\text{-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbomyl]-1H-pyrrole-1-heptanoic acid}$ calcium salt (2:1) having Formula 1:

5



Ca

2

10

is more suited to formulations and has been recommended as a drug.

United States patents 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,248,793; 5,280,126; 5,342,952, which are herein incorporated by reference, describe 15 various processes and key intermediates for preparing atorvastatin.

Atorvastatin calcium produced by the processes described in the above mentioned United States patents does not give amorphous atorvastatin consistently but gives a mixture of its crystalline and amorphous forms, which has unsuitable filtration and drying characteristics and are not suitable for large-scale production.

20 PCT application, WO 97/03959, discloses novel crystalline forms of atorvastatin calcium designated as Form I, Form II, and Form IV and method for their preparation which provide more favourable filtration and drying characteristics.

PCT application WO 97/03960 describes a procedure for converting the crystalline form of atorvastatin to the amorphous form. Process disclosed therein comprises dissolving crystalline form-I atorvastatin in a non-hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene. The process involves 5 complete removal of the solvent under high temperature (about 90°C) and high vacuum (about 5mm) using capital intensive equipment. Exposure of the material to high temperature for several days leads to degradation of the product. This makes the process very inconvenient to operate at a large scale. Slow removal of solvents at a manufacturing scale renders this process as inefficient cost-wise and less productive.

10

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide an efficient process for the production of amorphous atorvastatin, which eliminates the problems of prior art and is convenient to operate on a commercial scale.

15

Accordingly, the present invention provides a process for the preparation of atorvastatin calcium in an amorphous form which comprises dissolving crystalline atorvastatin in a non-hydroxylic solvent, adding a suitable non-polar hydro-carbon solvent and recovering atorvastatin from a solution thereof, by solvent precipitation, isolating and drying the product.

20

Generally, the product can be isolated by any standard method known in the art such as by filtration, centrifugation or decantation. Typically, this product is isolated by filtration when any of the solvents within the scope of the process are used.

Major advantages of the present invention compared to the prior art processes are:

- i. elimination of the need to remove solvent by drying techniques.
- ii. less time consuming with improved filtration.
- 5 iii. easy to operate on large-scale.
- iv. reproducibly produces amorphous product having allowable levels of residual solvents.

The present invention thus provides a novel process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises:

- 10 (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent;
- (b) adding a non-polar hydrocarbon anti-solvent to precipitate out the material; and
- (c) removing the solvent by filtration to afford amorphous atorvastatin calcium

15 The non-hydroxylic solvent is selected from a group of solvents, which have the ability to dissolve crystalline atorvastatin and includes tetrahydrofuran. Suitable non-polar hydrocarbon solvents are selected from a group consisting of: n-hexane, n-heptane, cyclohexane, hexane fraction, heptane fraction or the like. In a preferred embodiment of this invention, the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is n-hexane, cyclohexane or n-heptane.

20 Generally, crystalline atorvastatin calcium is dissolved in a non-hydroxylic solvent, e.g. tetrahydrofuran, at a concentration of about 15% w/v to about 40% w/v, preferably at a concentration of about 25% w/v to about 15% w/v at ambient

temperature and a non-polar hydrocarbon, preferably n-hexane, cyclohexane or n-heptane, is added at 0°C to 50°C, preferably at 20°C to 25°C. The product is recovered by filtration at ambient temperature. Filtration, which is fast and smooth, is carried out using nutsche filtration or centrifuge filtration. Preferably, nutsche filtration is used on large scale preparation. Filtered material, a semi-dry powder, is further dried to remove surface solvents in a vacuum tray drier, tray drier, fluid bed drier or a rotary vacuum drier to afford amorphous material. Preferably, material is dried in a vacuum tray drier at about 20°C to about 80°C for 6 hours to 24 hours. Most preferably, drying is carried out at about 50°C to about 60°C for 12 hours.

10 Quantity of antisolvent varies from 5 times to 50 times the input of crystalline atorvastatin calcium depending upon its solution in non-hydroxylic solvent. Preferably, the quantity of antisolvent used is about 20 times to about 40 times the input of crystalline atorvastatin calcium to make overall concentration of about 5% w/v to about 2.5 w/v%.

15 Amorphous atorvastatin calcium prepared according to the process of the present invention may be characterized by its x-ray powder diffraction pattern (Figures 2) as shown in the accompanied drawings. X-ray powder diffraction patterns (Figures 2) show no peaks which are characteristic of a crystalline atorvastatin calcium (Figure 1 of the accompanied drawings) thus demonstrating the amorphous nature of the product.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is the diffractogram of crystalline atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

Figure 2 is diffractogram of amorphous atorvastatin calcium. The horizontal axis represents 2θ and the vertical axis corresponds to peak intensity.

5

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

10

DETAILED DESCRIPTION OF THE INVENTION

Example 1

[R-(R*,R*)-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (Amorphous Atorvastatin calcium).

Method A

Crystalline atorvastatin calcium (10 kg) was dissolved in tetrahydrofuran (30 lt) under stirring at ambient temperature. Clear solution so obtained was added slowly to cyclohexane (350 lt) under nitrogen atmosphere. It was vigorously stirred maintaining temperature at 20-25°C. The precipitated product was centrifuged and dried under vacuum at about 60°C for 12 hours. Atorvastatin (9.5 kg) in an

amorphous form was obtained having residual solvent levels of 0.01% w/w tetrahydrofuran and 0.6% w/w cyclohexane. X-ray powder diffraction pattern (Figure 2 as shown in the accompanied drawings) demonstrate the amorphous nature of the product.

5

Method B

Crystalline atorvastatin calcium (10 kg) was dissolved in tetrahydrofuran (30 lt) under stirring at ambient temperature. To a clear solution of atorvastatin, cyclohexane (350 lt) was added under vigorous stirring at 20 to 25°C. The precipitated mass was further stirred for 30 minutes and filtered in a centrifuge. The product was dried under vacuum at about 60°C for 12 hours. Atorvastatin (9.6 kg) in an amorphous form was obtained having residual solvent levels of 0.01% w/w for tetrahydrofuran and 0.7% w/w for cyclohexane. X-ray powder diffraction pattern demonstrates the amorphous nature of the product.

10

15

Example 2

[R-(R*,R*)-2-(4-fluorophenyl)β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt
(Amorphous Atorvasatin calcium)]

20

The process of Example 1 was repeated with crystalline atorvastatin calcium (10 kg) dissolved in tetrahydrofuran (30 lt) and using n-hexane instead of cyclohexane

to give amorphous atorvastatin (9.5 kg.). X-ray crystallography confirmed the amorphous nature of the product.

Example 3

5 [R-(R*,R*)]-2-4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt
(Amorphous Atorvasatin calcium)

10 The process of Example 1 was repeated with crystalline atorvastatin calcium (10 kg) dissolved in tetrahydrofuran (30 lt) and using n-heptane instead of cyclohexane to give amorphous atorvastatin (9.6 kg). X-ray crystallography examination confirmed the amorphous nature of the product.

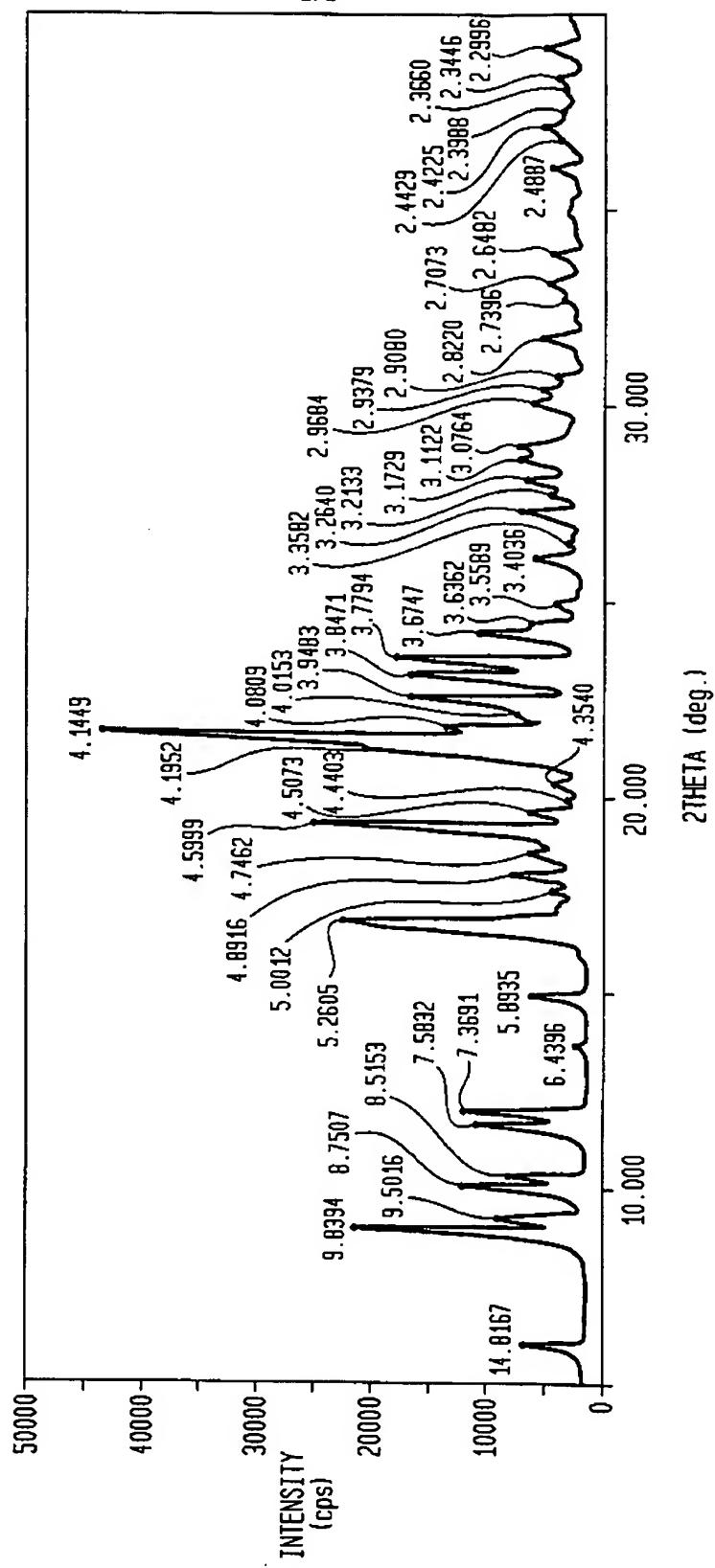
15 While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

WE CLAIM:

1. A process for the preparation of amorphous atorvastatin calcium and hydrates thereof which comprises:
 - (a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent;
 - (b) adding a non-polar hydrocarbon anti-solvent or adding the dissolved atorvastatin to the non-polar anti-solvent to precipitate out atorvastatin calcium; and
 - (c) removing the solvent by filtration to afford amorphous atorvastatin calcium.
2. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is chosen from a group of non-polar hydrocarbon solvents comprising n-hexane, cyclohexane or n-heptane.
3. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is n-hexane.
4. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is cyclohexane.
5. The process of claim 1, wherein the non-hydroxylic solvent is tetrahydrofuran and anti-solvent is n-heptane.
6. The process of claim 1, wherein said amorphous atorvastatin calcium is isolated by filtration.

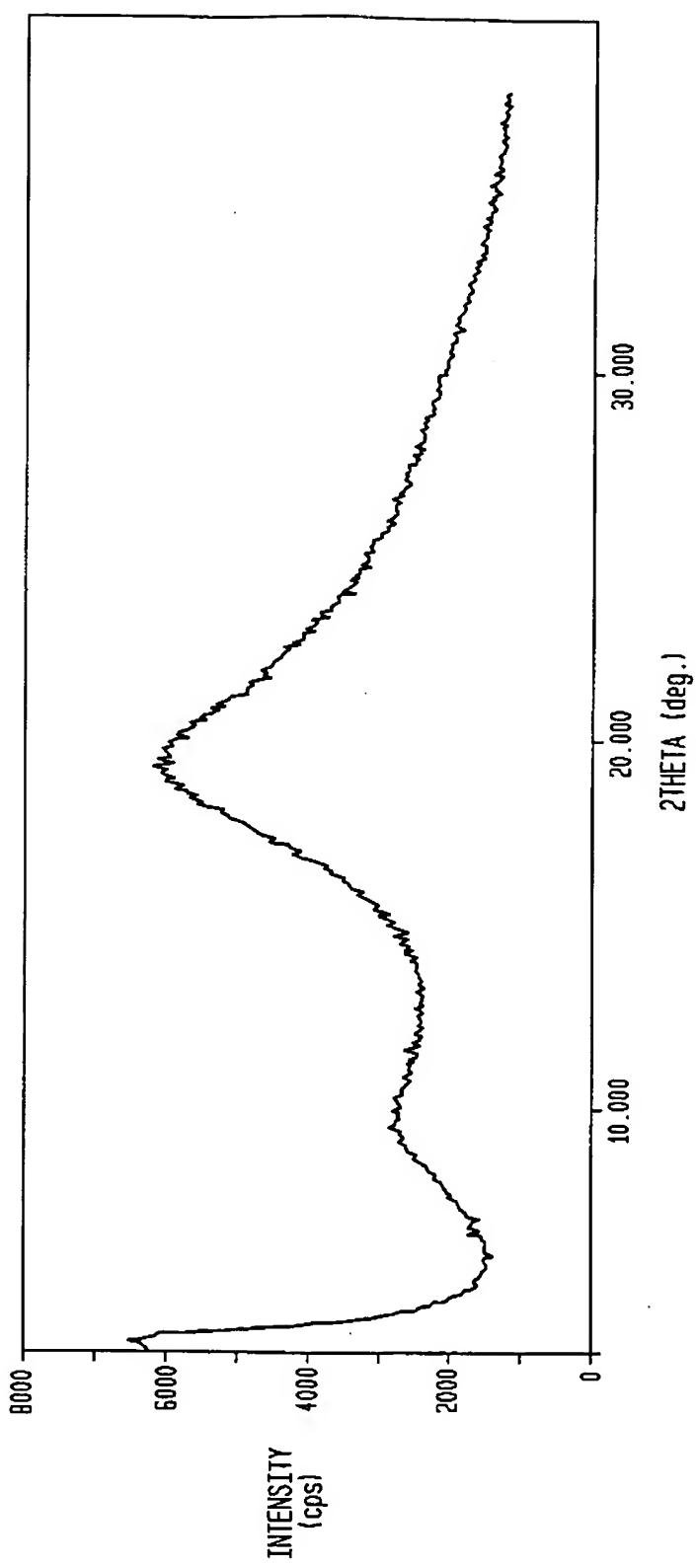
1/2

FIG. 1



2/2

FIG. 2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/00014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03959 A (WARNER LAMBERT CO ;BRIGGS CHRISTOPHER A (US); JENNINGS REX ALLEN () 6 February 1997 (1997-02-06) cited in the application	1-6
A	DE 33 27 449 A (GLAXO GROUP LTD) 2 February 1984 (1984-02-02) page 9, line 7 - line 16 page 12, line 10 -page 13, line 12	1-6
A	WO 97 03960 A (WARNER LAMBERT CO ;LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06) cited in the application claim 1	1-6
	----	----



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 May 2000

Date of mailing of the international search report

17/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/IB 00/00014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 03958 A (WARNER LAMBERT CO ;MCKENZIE ANN T (US)) 6 February 1997 (1997-02-06) cited in the application -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 00/00014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703959	A 06-02-1997	AU 6484296 A BG 102187 A BR 9609872 A CA 2220018 A CN 1190955 A CZ 9800121 A EP 0848705 A HR 960339 A HU 9900678 A IL 122118 A JP 11509230 T NO 980207 A PL 324496 A SK 6298 A US 5969156 A	18-02-1997 30-10-1998 23-03-1999 06-02-1997 19-08-1998 14-10-1998 24-06-1998 30-04-1998 28-07-1999 14-07-1999 17-08-1999 16-01-1998 25-05-1998 07-10-1998 19-10-1999
DE 3327449	A 02-02-1984	AT 382154 B AT 276783 A AU 566881 B AU 1741783 A BE 897422 A CA 1240313 A CH 657134 A CZ 280528 B CS 8305687 A CY 1434 A DE 3374010 D DK 68392 A DK 349083 A, B, EP 0107276 A ES 524590 D ES 8505689 A FI 832757 A, B, FR 2531087 A GB 2127401 A, B GR 79349 A HK 84288 A HU 190603 B IE 55748 B IL 69375 A IT 1168206 B JP 2025666 C JP 7030084 B JP 59044391 A KE 3805 A KR 9100046 B LU 84935 A MY 5887 A NL 8302705 A NO 832773 A, B, NZ 205083 A PL 243228 A PT 77135 A, B SE 453195 B SE 8304208 A SG 26088 G SI 8311558 A SK 403191 A	26-01-1987 15-06-1986 05-11-1987 02-02-1984 30-01-1984 09-08-1988 15-08-1986 14-02-1996 15-03-1988 02-09-1988 12-11-1987 25-05-1992 31-01-1984 02-05-1984 01-06-1985 01-10-1985 31-01-1984 03-02-1984 11-04-1984 22-10-1984 28-10-1988 29-09-1986 02-01-1991 31-12-1986 20-05-1987 26-02-1996 05-04-1995 12-03-1984 03-06-1988 19-01-1991 23-11-1983 31-12-1987 16-02-1984 31-01-1984 14-03-1986 27-08-1984 01-08-1983 18-01-1988 31-01-1984 15-07-1988 31-12-1995 11-07-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten. Application No.
PCT/IB 00/00014

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE 3327449	A	SU	1266471 A	23-10-1986
		US	4994567 A	19-02-1991
		US	5013833 A	07-05-1991
		US	4562181 A	31-12-1985
		US	4820833 A	11-04-1989
		YU	155883 A	30-04-1986
		ZA	8305579 A	26-09-1984
		ZW	17383 A	26-10-1983
WO 9703960	A	06-02-1997	AU	700794 B
			AU	6497896 A
			BG	102188 A
			BR	9609714 A
			CA	2220455 A
			CN	1190956 A
			CZ	9800122 A
			EP	0839132 A
			HR	960312 A
			IL	122161 A
			JP	11510486 T
			NO	980209 A
			PL	324463 A
			SK	5898 A
WO 9703958	A	06-02-1997	AU	6484196 A
			BG	102186 A
			BR	9610567 A
			CA	2220458 A
			CN	1190957 A
			CZ	9800123 A
			EP	0848704 A
			HR	960313 A
			HU	9901687 A
			IL	122162 A
			JP	11509229 T
			NO	980208 A
			PL	324532 A
			SK	5998 A